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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,682	PERRICAUDET ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *6,27,35 and 37-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-26,28-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/894,246.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 9-6-07 has been entered. Claims 2, 3, 21 and 22 have been amended. Claims 1-44 are pending. Claims 1-5, 7-26, 28-34 and 36 are under consideration.

Information Disclosure Statement

1. The information disclosure statement filed 4-14-04 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. There are **two pages of form PTO-892** in the submitted IDS, which is improper. The IDS must have **(3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement.** Appropriate correction is required.

2. The information disclosure statement filed 4-14-04 fails to comply with 37 CFR 1.98(a)(2), which **requires a legible copy** of each cited foreign patent document; each non-

patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Applicants respond that it seems all of the documents marker as "not considered" have been included on "Notice of References Cited" pages. It should be noted that if applicants would like the references cited in form PTO-892 and the search report to be considered, submission of a proper form PTO-1449 and legible copy of the cited references is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3, 22, 34 and 36 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention and is repeated for the reasons set forth in the preceding Official action mailed 3-6-07. Applicant's arguments filed 9-6-07 have been fully considered but they are not persuasive.

Applicants argue that one of skilled in the art was familiar with examples of these antibodies, aFGF and bFGF, therefore, these abbreviations are suffices under the circumstances (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 3-6-07. These terms are abbreviation that can stand for various meanings. It is unclear what meaning is intended. Spelling out the terms would be remedial.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5, 7-26, 28-34 and 36 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing CD4+, CD3+ and CD8+ T cells by the combination of anti-CD3 or anti-CD4 antibody with Ad-βgal-gp19K expressing gp19K protein of adenovirus, decreasing cytotoxic activity of splenocytes, isolated

from animals treated with anti-CD4 antibody and Ad-βgal-gp19K, on p815-β-gal target cells expressing β-galactosidase, and prolonging the expression of β-gal in a liver of a mouse with the combination of anti-CD4 antibody and Ad-βgal-gp19K, does not reasonably provide enablement for a composition comprising any immunosuppressive agent, such as anti-CD4 antibody, and a recombinant adenovirus containing a first recombinant DNA encoding a therapeutic protein, such as aFGF, and a second recombinant DNA encoding an adenoviral gp19k protein, and a method for expression of a sequence of interest by using said composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 3-6-07. Applicant's arguments filed 9-6-07 have been fully considered but they are not persuasive.

Applicants argue that claims 1-5, 7-18 and 34 recite a composition and one use would be in vivo gene therapy, however, the composition can be used for in vitro or other methods or studies. Therefore, there is no need to show a "therapeutic effect". No trial and error experimentation is required to use the claimed composition (amendment, p. 8-9). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 3-6-07. The specification states "[t]he present invention relates to the field of gene therapy and in particular to the use of adenovirus for expressing a therapeutic gene of interest. It relates, more specifically, to a novel method for treating pathologies of genetic origin, which method is based on the combined use of two types of therapeutic agents." (specification, p. 1, first paragraph). It appears that the use of the claimed composition for gene therapy in vivo is the sole use of said composition. The claims read on gene therapy in vivo in light of the specification. B-gal was

known in the art at the time of the invention as a marker gene rather than a therapeutic gene. The specification of the present application fails to provide adequate guidance and evidence that an adenovirus vector as claimed in the present application expressing a gene of interest, such as aFGF, and an adenoviral gp19k protein as separate proteins or as a fusion protein in combination with an immunosuppressive agent, such as anti-CD4 antibody could provide therapeutic effects for a gene therapy in a subject *in vivo*. The specification also fails to provide adequate guidance and evidence for the correlation of a specific gene of interest, such as aFGF, with a particular disease or disorder such that the administration of the adenovirus expressing said gene of interest would provide therapeutic effects for a gene therapy in a subject *in vivo*. Applicant fails to point out where in the specification has support for the in vitro use or other methods or studies of the claimed composition.

Applicants argue that the sequence of gp19k protein was known in the art. Applicants cite page 13, line 9 to page 14, line 5 and Example 2.3 and argue that mice administered an adenoviral vector of the claimed invention show a lack of inflammatory reaction and a prolonged expression period. Applicants further argue that the cited references Eck and others relate to clinical standards, which are the realm of the FDA, and not the PTO standard, and nothing in these papers says that gene therapy is devoid of promising inventions or devoid of any patentably, pharmaceutical properties akin to those discussed in In re Brana (amendment, p. 9-11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 3-6-07 and the reasons set forth above. The state of the art of gene therapy in vivo was unpredictable at the time of the invention. The cited references Eck and others show that the Achilles heel of gene therapy is gene delivery and the problem has been an inability to deliver

genes efficiently and to obtain sustained expression. Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. These factors include the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA. These factors differ dramatically based on the vector used, and the disease being treated. The cited Eck and other references demonstrate unpredictable nature of gene therapy in vivo in general, which is PTO standard rather than FDA standard.

Further, the specification only discloses the prolonged expression of β-gal in the liver of a mouse but fails to provide adequate guidance and evidence for the prolonged expression of any therapeutic gene in organs other than liver in a subject *in vivo*. Different organs, tissues or targeted site could vary physically and biologically such that the expression of a gene *in vivo* also could vary depending on the site being targeted. It is unclear whether the adenoviral gp19k gene and anti-CD4 antibody could provide sufficient expression in a particular organ, tissue or targeted site such as to achieve prolonged expression of a gene of interest so as to provide therapeutic effect in a subject for a gene therapy of a particular disease or disorder. Thus, the claims remain rejected under 35 U.S.C. 112 first paragraph.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-5, 7-17, 19-23, 25, 26, 28-34 and 36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leibowitz et al., 1994 (WO 94/16065, IDS) in view of Pearson et al., 1993 (Clinical Experimental Immunology, Vol. 92, p. 211-217) and Nabel et al., 1994 (Annals New York Academy of Sciences, Vol. 714, p. 247-252) and is repeated for the reasons set forth in the preceding Official action mailed 3-6-07. Applicant's arguments filed 9-6-07 have been fully considered but they are not persuasive.

Applicants argue that none of the cited references teach the claimed composition and there is no motivation to combine the cited references. There is nothing in any of the references suggesting the prolonged expression resulting from the combination compositions claimed. Applicants further argue that it is hindsight combination of the present invention (amendment, p. 11-12). Although none of the cited reference teaches all the elements of the claimed composition, however, Leibowitz teaches E19pk protein can alter the presentation of MHC class I cell surface antigen to reduce transplant rejection by the recipient organism's immune system

and Pearson teaches that immunosuppressive agent such as anti-CD4 antibody can induce prolonged allograft survival in adult mice. Nabel teaches using recombinant adenoviral vector expressing FGF-1 for gene transfer into vascular cells and discloses the problem of host immune response to the adenoviral vector for gene transfer. The teachings of Leibowitz and Pearson show that E19pk protein and anti-CD4 antibody can reduce host immune response. Since Nabel teaches using recombinant adenoviral vector expressing FGF-1 for gene transfer into vascular cells and discloses the problem of host immune response to the adenoviral vector for gene transfer, it would be obvious for one of ordinary skill in the art to combine the immunosuppressive agent, such as anti-CD4 antibody, with an adenovirus vector expressing FGF-1 and gp19k proteins in a composition and the use of said composition. Further, the claims do NOT recite prolonged expression resulting from the combination composition as claimed. There is sufficient motivation for one of ordinary skill in the art to combine the cited references in view of the teachings of Leibowitz, Pearson and Nabel with reasonable expectation of success.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Thus, the claims remain rejected under 35 U.S.C. 103(a).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Shin-Lin Chen, Ph.D.